Guidance for Industry

Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device; Guidance for Industry and FDA

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This document supersedes "Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device; Draft Guidance for Industry and FDA" dated February 7, 2002.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Restorative Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document was developed as a special control guidance to support the classification of the resorbable calcium salt bone void filler device into class II (special controls). The device, as proposed, is intended to fill bony voids or gaps caused by trauma or surgery that are not intrinsic to the stability of the bony structure. This guidance is issued in conjunction with a Federal Register notice announcing the classification of the resorbable calcium salt bone void filler device.

Following the effective date of this final classification rule, any firm submitting a 510(k) premarket notification for a resorbable calcium salt bone void filler device will need to address the issues covered in the special control guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the resorbable calcium salt bone void filler device. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act),

including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with the resorbable calcium salt bone void filler device identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device. (See also 21 CFR 807.85).

This special control guidance document identifies the classification regulation and product code for the resorbable calcium salt bone void filler device (Refer to Section 4 – **Scope)**. In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with the resorbable calcium salt bone void filler device and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[1]," a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a special controls guidance document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should

[1] http://www.fda.gov/cdrh/ode/parad510.html

describe how this special control guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this guidance document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this class II special controls guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 8 for specific information that should be included in the labeling for devices of the types covered by this document.)

Summary report

We recommend that the summary report contain:

?? Description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.[2]

?? Description of device design requirements.

?? Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)

?? Discussion of the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

?? A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6-8 of this class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

?? If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information refer to the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special controls guidance document to a premarket notification for a resorbable calcium salt bone void filler device.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 888.3045 (product code: MQV). The classification identification below identifies the device as it existed prior to May 28, 1976.

§888.3045 Resorbable calcium salt bone void filler device.

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[3] If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[4] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

(a) Identification. A resorbable calcium salt bone void filler device is a resorbable implant intended to fill bony voids or gaps of the extremities, spine, and pelvis that are caused by trauma or surgery and are not intrinsic to the stability of the bony structure.

(b) Classification. Class II (special controls). The special control for this device is the FDA guidance document entitled "Class II Special Controls Guidance Document: Resorbable Calcium Salt Bone Void Filler Device; Guidance for Industry and FDA."

Bone void filler devices composed of alternate materials may be demonstrated to be substantially equivalent under section 510(k) of the Act to the resorbable calcium salt bone void filler device identified in this guidance document. However, this guidance document does not specifically address the type of other information that may be applicable to devices composed of alternative materials.

This guidance document is not intended to address devices composed of calcium salts derived from a biological source (e.g., either animal or human tissue), or calcium salt additives derived from a biological source. This guidance document is also not intended to address use of the device in filling bony voids or gaps that, in the absence of the bone void filler, would require stabilization or fixation for stabilization (e.g., cast, internal fixation, external fixation, or other internal or external stabilization methods) to prevent collapse.

5. Risks to Health

In the table below, FDA has identified the risks to health generally associated with the use of the resorbable calcium salt bone void filler device addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
infection of the soft tissue and/or bone (osteomyelitis)	**Section 9**
adverse tissue reaction	**Section 8**
transient hypercalcemia	**Sections 7, 10**
incomplete bone formation or lack of bone formation	**Sections 7, 10**
delayed union	**Sections 7, 10**
nonunion	**Sections 7, 10**
fracture of the bone void filler with or without particulate formation	**Sections 7, 10**
device migration or extrusion	**Sections 7, 10**
fracture of the newly formed bone	**Sections 7, 10**

6. Device Description

FDA recommends that you provide the following to describe your device.

A. Chemical Composition of Device

We recommend that you provide the following information about the chemical composition of the device:

- identification of the device material(s), including all additives, along with their respective amounts
- identification of the crystalline and non-crystalline phases, phase purity, and the weight percentage of phases, using X-ray diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FTIR)
- elemental analysis, identifying the cation to anion ratio (e.g., Ca/P, Ca/S) and all trace impurities
- diffraction patterns along with superimposed patterns of each phase as given for the relevant calcium salt available from the International Center for Diffraction Data/ Joint Committee on Powder Diffraction Standards (ICDD/JCPDS).

We recommend that you use the applicable voluntary consensus standards listed below to establish the material characteristics of your device:

- ASTM F1185, "Standard Specification for Composition of Ceramic Hydroxylapatite for Surgical Implants"
- ASTM F1088, "Standard Specification for Composition of Beta-Tricalcium Phosphate for Surgical Implantation"
- United States Pharmacopoeia (USP) National Formulary (NF) "Official Monograph for Calcium Sulfate"

B. Physical Properties of Device

We recommend that you provide the following information about the physical properties of the device:

- identification of the physical form of the device (e.g., granules, pre-formed block, or putty/paste intended to set *ex-vivo* or *in-vivo)*
- dimensional specifications for all device configurations
- for irregularly shaped devices (other than irregularly shaped granules), device drawings or photographs
- specification of device mass, volume and density
- specification of device porosity (e.g., total porous volume, pore diameter, interconnectedness).

7. Device Performance Characteristics

FDA recommends that you provide the information below to evaluate the device performance characteristics.

A. Performance Testing - Bench

We recommend the following performance tests using final, sterilized devices and simulating the intended physiological environment:

- pH testing[5]
- dissolution/solubility testing compared to the predicate device[5]

For a device intended to set *in-vivo,* we recommend that you also evaluate:

- working time
- setting time
- dimensional stability
- setting reaction temperature
- pH
- chemical analysis of the final device.

For injectable devices, we recommend that you also evaluate injectability testing and pressure testing or analytical assessment of pressures expected upon injection of the device into the defect site.

B. Performance Testing – Animal

Whether animal performance testing is necessary will depend upon how similar the material and performance characteristics are compared to those of the predicate device.

For devices that have the same critical specifications (i.e., chemistry, crystallinity, physical form, porosity, dissolution/solubility) and the same intended use as the predicate device, information on material characterization and bench performance testing (Sections 6 and 7A, above), directly compared to the predicate device, may be sufficient to demonstrate substantial equivalence.

For devices that do not have the same critical device specifications, we recommend that you evaluate device performance in an animal model that, in addition to incorporating generally accepted scientific principles, also takes into consideration the following specific study design issues:

- use of an animal model that is representative of the indications for use, the full range of anatomical sites proposed for use, and specifically how the device is to be used
- use of skeletally mature animals and a critical size defect
- use of the predicate device and/or autogenous bone graft as the positive control group(s) and use of an empty defect as a negative control
- use of radiography, histology, and histomorphometry to assess bone formation and device resorption at various, relevant time points over the course of healing, in

[5] If animal performance data are available and adequately address bone formation and device resorption, bench testing relating to pH and device dissolution/solubility may not be necessary.

addition to supportive biomechanical testing of the new bone formed

?? use of an adequate study duration to demonstrate bone healing and the effects of any residual device material.

8. Biocompatibility

FDA recommends that you conduct biocompatibility testing as described in the FDA-modified **Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing**, http://www.fda.gov/cdrh/g951.html for blood-contacting, long-term implanted devices. We recommend that you select biocompatibility tests (Parts 5 and 10 of ISO-10993) appropriate for the duration and level of contact with your device. If *identical* materials are used in a predicate device with the same type and duration of patient contact, you may identify the predicate device in lieu of biocompatibility testing.

9. Sterility

FDA recommends that you provide sterilization information in accordance with the **Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/361.html. The device should be sterile with a sterility assurance level (SAL) of 1×10^{-6}.

10. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).[6]

Directions for Use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we expect to see clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Intended Use/Indications for Use

We recommend that you provide a statement of the intended use/indications for use for your device.

Instructions for Use

Instructions for use should include adequate information (contraindications, warnings, and precautions) to address the identified risks to health. In addition to these general issues, we recommend that you address the following points, as applicable, to your

[6] Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801.

device:

- instructions for proper placement and containment in the desired treatment area
- instructions on the need for adequate fixation
- a precaution against implanting the resorbable calcium salt bone void filler device in a patient with a pre-existing calcium metabolism disorder (e.g., hypercalcemia)
- a precaution against over-filling the defect site
- a warning against use in infected sites (for devices that do not resorb rapidly).

For block devices, we also recommend that you provide instructions on whether the device may be cut or shaped at the time of use. If the device may be cut or shaped, we recommend that the labeling identify appropriate precautions to assure that debris will not restrict the pores of the device as it is cut, e.g., a precautionary statement for the user to ensure that any shaped device surfaces are smooth and free from excessive loose particles.

For devices intended to set *ex vivo* or *in vivo,* we recommend that you address the following additional points:

- a precaution against adding any additional substances other than those provided (in the absence of data on the use of the device mixed with other substances)
- a specification of product working time and setting time
- any special instructions with respect to drying the surgical field and/or not irrigating the defect site prior to final setting of the device (for a device intended to set *in vivo*)
- a precaution against disturbing the device (over a specified time frame) once it begins to harden
- instructions on how and when excess material should be removed from the defect site.

For devices intended for injection into the defect site, we recommend that you address the following additional points:

- a precaution against over-pressurizing the device because this may lead to extrusion of the device beyond the site of its intended application and damage to the surrounding tissues.
- a precaution against over-pressurizing the defect site since this may lead to fat embolization or embolization of the device material into the bloodstream.